

Allergic Emergencies Encountered by the Dermatologist

Severe Cutaneous Adverse Drug Reactions

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Introduction

Cutaneous adverse drug reactions (ADRs) are the most frequent ADRs, affecting about 3% of hospitalized patients (1). The rate of severe cutaneous ADRs resulting in death or disability is fortunately low (1 for 1000 hospitalized patients [2]). Nevertheless, these events constitute emergencies that should be promptly recognized and treated. Cutaneous ADRs are most often an erythematous macular and/or papular rash, which fade in a few days. Those clinical features can be the initial presentation of severe cutaneous ADRs. In this short article, we will focus on such severe events. Acute exanthematous generalized pustulosis (3) will be voluntarily excluded from the discussion. Indeed, although spectacular, this drug-induced eruption is exceptionally life-threatening. Briefly, this entity is characterized by the sudden and usually simultaneous onset of a high fever and a widespread edematous scarlatiniforme rash, soon covered by hundreds of nonfollicular, small, superficial pustules associated with a frank hyperleukocytosis (Fig. 1). Acute generalized exanthematous pustulosis is remarkable by its short time to the onset after the administration of the suspected drug (<24 h), the great predominance of antibiotics as causative agents, and its rapid spontaneous healing (Table 1). On the other hand, Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), hypersensitivity syndrome, serum sickness and vasculitis, and angioedema are really life-threatening diseases and will be discussed herein.

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Fig. 1. Acute exanthematous generalized pustulosis with nonfollicular superficial pustules.

Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN)

Nosology

In 1922, Stevens and Johnson (4) described two febrile children with erosive stomatitis, severe conjunctivitis, and disseminated cutaneous eruption distinct for these authors from erythema multiforme. In his 1956 article (5), Lyell described four patients with a "scalded skin" appearance owing to drug therapy, staphylococcus, and idiopathic causes. In fact, this original article included two completely different diseases: staphylococcal scalded skin syndrome (SSSS) and TEN, which now constitute two well-separated entities. TEN is now considered as a drug-induced reaction (6–8). It soon became evident that severe forms of SJS could lead to TEN and that both diseases could be induced by the same drugs. The similarities between the histopathological findings and the culprit drugs suggest that SJS is the minimal form of TEN spectrum (9). Since target-like lesions are present in most TEN cases around the areas of epidermal sloughing, by analogy many persons included SJS and TEN into the erythema multiforme spectrum, resulting in confusion. In fact, TEN spectrum and erythema multiforme spectrum are distinguishable (10). Clinical features are different: patients with erythema multiforme major have typical targets (Fig. 2), mainly on the extremities but patients with SJS have widely distributed purpuric macules and blisters, mainly



Fig. 2. Typical targets in erythema multiforme major.

on the trunk and face. Etiologies are different: erythema multiforme major mainly occurs after herpes simplex and mycoplasma infections, and SJS is mainly drug-induced. The prognoses are different: erythema multiforme is usually benign and SJS can evolve to life-threatening TEN.

Epidemiology of SJS and TEN

Cases of SJS and TEN remain very rare. The incidence appears to be about 1 case/million per year (11–15). TEN has been observed worldwide and has been described in all human populations.

The risk of developing TEN is considerably increased in HIV-infected patients. The incidence of SJS and TEN during acquired immunodeficiency syndrome (AIDS) has been evaluated to be 1/1000 person/yr (16,17). Two explanations have been proposed for this finding: (1) the greatly increased number of drugs used in AIDS patients compared with other patients and (2) the HIV infection itself with its virus-induced immunodeficiency and associated infections.

The incidence of TEN among patients with bone marrow transplantation has not been evaluated, but TEN appears to be not as infrequent as previously thought in bone marrow recipients (18). TEN in bone marrow recipients seems to be related to a drug reaction (to sulfonamides or to other antibiotics) as often as to graft vs host disease. Several cases of TEN have been reported in patients with systemic lupus erythematosus (19). The simultaneous occurrence of these two diseases is rare, but too frequent to be a simple coincidence.

Culprit Drugs in SJS and TEN and Pathophysiology

A case-control study, the SCAR study (20), has confirmed the responsibility of the "classical culprit" drugs antibacterial sulfonamides (cotrimoxazole), aromatic anticonvulsants (phenobarbital, phenytoin, carbamazepine), some antibiotics (aminopenicillins, quinolones, cephalosporins), some nonsteroidal anti-inflammatory agents (phenylbutazone, oxyphenbutazone, isoxicam, piroxicam), chlormezanone, and allopurinol. The risks inherent to the above-mentioned drugs have been estimated to be between 0.2 cases/million users in a week for aminopenicillins and 4.5/million users in a week for sulfonamides.

In adult patients who are receiving anticonvulsants, TEN is often associated with concurrent radiotherapy or chemotherapy for malignant cerebral tumors. Owing to a common metabolic pathway, phenobarbital, phenytoin, and carbamazepine may induce crossreaction, and all three drugs should be contraindicated following TEN owing to one of these agents (20). Many drugs have been reported as the inducer of TEN in at least one observation. The culpability of antibiotics, analgesics, and antipyretics is often difficult to assess because these drugs are prescribed for flu-like symptoms that could be early symptoms of TEN.

SJS and TEN are generally considered to be a cell-mediated cytotoxic reactions against keratinocytes since the epidermis is infiltrated with activated lymphoid cells mainly of CD8 type (21). Apoptosis appears to be the mechanism of keratinocyte death in TEN (22). The time interval between the beginning of drug intake and the reaction (mean time of 9 d for the first occurrence, and a few hours in recurrences) is consistent with immunologic mechanisms. SJS and TEN induced by sulfonamides and anticonvulsants have also been proven to be linked with a defect in the detoxification of the culprit drug-reactive metabolites (23). The immune reaction could be directed against drug-reactive metabolites produced in excess.

Clinical Aspects, Course, Diagnosis, and Prognosis

The cutaneous lesions begin with a burning and painful eruption. This eruption extends symmetrically from the face and upper part of the body to entire body, predominating on the trunk and proximal limbs. Maximal extension of lesions usually occurs in 2 or 3 d, and sometimes a few hours. Cases with epidermal detachment <10% are classified as SJS, above 30% as TEN, and cases with areas of epidermal detachment between 10 and 30% as overlap SJS-TEN. Sheet-like loss of epidermis and flaccid blisters spreading with pressure occur in TEN. Nikolsky's sign—dislodgment of epidermis by lateral pressure—

is positive over large areas involved by confluent erythema (Fig. 3). Traumatized sites leave a dark-red oozing dermis. The entire skin surface may be involved with up to 100% of the epidermis sloughing. Mucous membrane involvement is present in nearly all patients of the SJS-TEN spectrum. Widespread painful erosions result in impaired alimentation, photophobia, and painful micturition. Pseudomembranous conjunctival erosions have a tendency to form synechiae between eyelids and conjunctiva. Fever is usual. Asthenia, skin pain, and anxiety are extreme. Gastrointestinal or tracheo-bronchial epithelium can be involved by a necrosis process, resulting in a profuse diarrhea or in respiratory distress, respectively, causing high morbidity (24,25). Blood abnormalities are almost always present. Anemia and lymphopenia are found in virtually all patients, neutropenia in 30% indicating a poor prognosis, and thrombopenia in 15%. Prerenal azotemia is common (26). Fluid losses are massive with electrolyte imbalance. During the first days, skin lesions are usually colonized by *Staphylococcus aureus*. Later they are invaded by Gram-negative rods. Thermoregulation is impaired, and energy expenditure is increased. Alteration of immunologic functions increases the likelihood of sepsis. Re-epidermization begins after a few days, and most of the skin surface is re-epithelialized in 3 wk. Scarring may occur in areas of pressure or infection. Disturbances in pigmentation are inevitable with a patchwork of pigmented and hypopigmented areas. Ocular sequelae are frequent and severe. In TEN, 40% of survivors are affected. Patients may have watery eyes because of the obstruction of the tear, but most have dryness resulting from a Sjögren-like sicca syndrome (27). Photophobia, burning eyes, visual impairment, and even blindness may result. Abnormal nail regrowth, phimosis, and vaginal synechiae may be present.

Diagnosis of SJS and of TEN is clinically evident in most cases, but a skin biopsy and direct immunofluorescence studies should be performed to exclude bullous diseases not related to drug therapy. The typical pathologic lesions show full-thickness necrosis of epidermis, which is detached from a little-altered dermis. Immunofluorescence studies are negative. Exfoliative, pustular, and blistering diseases can be misdiagnosed with SJS or TEN. Exfoliative dermatitis is a generalized erythema with scaling in large sheets on palms and soles. SSSS is an extensive subcorneal separation of the stratum corneum caused by staphylococcal toxins. Acute exanthematous pustulosis discussed in the introduction can by coalescence of pustules lead to superficial exfoliation. Paraneoplastic pemphigus, Ig A linear dermatosis may be confused with SJS and TEN. Direct immunofluorescence studies make the diagnosis (28,29). Chemical and thermal

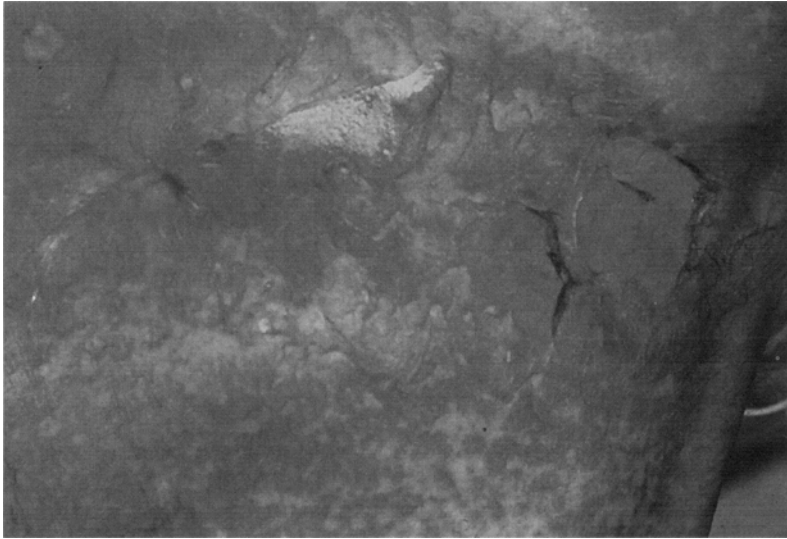


Fig. 3. Sheetlike loss of epidermis in toxic epidermal necrolysis.

burns, and blisters in comatose patients may be confused clinically and pathologically with TEN.

SJS is fatal in about 5% of case and TEN in about 30%. The predominant cause of death during TEN is infection. The most important factors of prognosis are the age, the percentage of denuded skin, the serum urea nitrogen level, and visceral involvement.

Management of SJS and TEN (30)

SJS and TEN are life-threatening diseases and the management of patients must be prompt. First, the physician must recognize SJS and TEN early and withdraw all potential culprit drugs, i.e., all drugs introduced within 1 mo. Second, iv-fluid replacement must be initiated, and the patient transferred to an intensive care unit or a burn center. Medical transport requires pain control, iv fluid replacement, aseptic handling, sterile fields, and avoidance of any adhesive material. Principles of symptomatic treatment are the same as for burns, fluid replacement, nutritional support, and antimicrobial policy.

To date there is no specific treatment for TEN. Effectiveness of corticosteroids early in the disease have been advocated, but never demonstrated in controlled trials. Retrospective studies demonstrate no benefit of corticosteroids or higher rates of morbidity and mortality in TEN patients treated with corticosteroids (31). Corticosteroids are not recommended and should be avoided. Plasmapheresis, cyclosporine, cyclophosphamide, and monoclonal antibodies (MAbs)

against cytokines have been used in isolated cases reports. The results of these uncontrolled studies must be interpreted with skepticism (32–34). Thalidomide has been shown to be detrimental in the only controlled study in TEN treatment (35). The value of iv immunoglobulin should be confirmed in a randomized, placebo-controlled study (36).

Hypersensitivity Syndrome (Drug Rash with Eosinophilia and Systemic Symptoms [DRESS])

Nosology

Most skin adverse drug reactions are considered pathophysiologically as “hypersensitivity reactions” to drugs, but the term “hypersensitivity syndrome” is misleading and can be a matter of clinical confusion if it regroups reactions as different as erythroderma, exfoliative dermatitis, acute generalized exanthematous pustulosis, systemic lupus erythematosus-like reaction, SJS, TEN, or pseudolymphoma. The term “hypersensitivity syndrome” should be restricted to mucocutaneous eruption and fever with frequent lymphadenopathy, hepatitis, and eosinophilia, excluding well-defined entities as SJS/TEN or acute generalized exanthematous pustulosis (37). The acronym “DRESS” for drug rash with eosinophilia and systemic symptoms clarified the nosology (38).

Culprit Drugs in Hypersensitivity Syndrome and Pathophysiology

Data in the literature appreciating the incidence of hypersensitivity syndrome are lacking. For the three main aromatic anticonvulsants (phenytoin, carbamazepine, phenobarbital), the incidence of hypersensitivity syndrome has been estimated to 1 reaction/10,000 exposures. Sulfonamides, and among them dapsone (39), are also one of the most frequent causes of this syndrome. Other drugs, such as allopurinol, gold salts, and sorbinil, have also been implicated. Detoxification defects have been implicated in the pathophysiology of anti-convulsant- and sulfonamide-induced hypersensitivity syndrome. These detoxification defects seem to be constitutional and inherited. For anticonvulsants, an inability to detoxify toxic arene oxide metabolites seems to be a risk factor. Crossreactivity among the three main aromatic anticonvulsants has been well documented clinically and in vitro (40). For sulfonamides, patients’ slow acetylator phenotype and an in vitro susceptibility of patients’ lymphoid cells to correspondent toxic hydroxylamine are risk factors to develop an hypersensitivity syndrome to these drugs.



Fig. 4. Infiltrated rash during hypersensitivity syndrome.

Clinical Aspects, Course, Diagnosis, and Prognosis

The most frequent clinical features of hypersensitivity syndrome are fever and rash. Rash often begins as a morbilliform eruption of benign aspect. This rash may become indurated and infiltrated with

facial swelling and exfoliative dermatitis with sometimes bullous or purpuric skin lesions (Fig. 4). Arthritis may appear. Blood abnormalities and among them eosinophilia and monucleosis-like atypical lymphocytosis are common and appear in about 30% of cases. Systemic complications may occur: hepatitis in about 50% of cases, interstitial nephritis in about 10% of cases, and less frequently heart, lung, thyroid, and brain involvement.

Pathologic lesions show a lymphoid infiltrate sometimes with an epidermotropism and atypical cells consistent with the diagnosis of "pseudolymphoma." Viral infections, such as Epstein-Barr virus, may be difficult to distinguish from hypersensitivity syndrome. Serum sickness and drug-induced vasculitis, which we will describe later, may constitute differential diagnosis of hypersensitivity syndrome.

Recovery from hypersensitivity syndrome is usual, but rash and hepatitis may persist for weeks. It may be fatal, especially in cases of severe hepatitis (41). We have evaluated the mortality rate of such a reaction at about 8% (unpublished data). Usually atypical lymphoid hyperplasia or pseudolymphoma resolves with the withdrawal of the drug, and exceptionally real lymphoma may follow the acute phase (42).

Management of Hypersensitivity Syndrome

Hypersensitivity syndrome must be promptly recognize and all potential culprit drugs withdrawn. The typical delay after the beginning of a drug and the onset of the reaction is 2–6 wk. Corticosteroid therapy has been widely used without controlled studies. In our experience, systemic corticosteroids (0.5–1 mg/kg) dramatically improve symptoms and laboratories measurements. Relapses of reaction may occur as corticosteroids are tapered. In anticonvulsant hypersensitivity syndrome, one must keep in the mind that a crossreactivity exists among the three main aromatic anticonvulsants: phenytoin, carbamazepine, phenobarbital. Therefore, it may be difficult to find alternative anticonvulsant therapy.

Vasculitis and Serum Sickness

Nosology

Vasculitis results in an inflammation and necrosis of the blood vessel wall. Among the different causes of vasculitis, drugs are cited. Drug-induced vasculitis represents about 10% of acute cutaneous vasculitis (43). They usually involve small vessels. This vasculitis is thought to result from antibodies directed against drug-related hapten. Serum

sickness, originally described with horse serum, is thought to result from the deposition of immune complexes in small vessels, and then complement activation and granulocytes recruitment.

Culprit Drugs in Vasculitis and Serum Sickness

Drugs often associated with vasculitis are allopurinol, penicillin and aminopenicillins, sulfonamides, thiazide diuretics, pyrazolones, hydantoins, and propylthiouracil (44). More recently, retinoids, quinolones, and immunotherapeutics agents have been involved (45–47). Serum sickness was originally described with horse serum containing diphtheria antitoxin. Serum sickness has since been noted with horse antithymocyte globulins or human diploid cell rabies vaccine (48,49). Serum sickness-like reactions have been also induced by cefaclor, minocycline, penicillins, and streptokinase (50–53).

Clinical Aspects, Course, Diagnosis, and Treatment

Typically vasculitis is clinically represented by a palpable papular purpura predominating on the lower extremities (Fig. 5). Less frequently, hemorrhagic blisters, urticaria, ulcers, nodules, Raynaud's disease, and digital necrosis may occur. The skin may not be solely involved. Involvement of the kidney, the liver, gastrointestinal tract, or nervous system may be present and be life-threatening.

Serum sickness presents as an erythema first affecting fingers, toes, and hand, and then becoming a morbilliform eruption with sometimes urticaria. Fever, general symptoms, arthralgia, and arthritis are the most frequent features. Visceral involvement is present in half the cases.

In vasculitis, histology shows small dermal vessels with fibrinoid necrosis, infiltrate by polymorphonuclear leukocytes and nuclear dust. Direct immunofluorescence exhibits deposits of IgM and C3 complement on capillary walls. Vasculitis typically develops 7–21 d after onset of a new drug.

Serum sickness is characterized by a decrease in serum C3 and C4 complement levels. During serum sickness-like reactions, serum complement levels are not reduced. Drug-induced vasculitis is difficult to diagnose. Other forms of vasculitis should be eliminated: Schönlein-Henoch purpura in young patients, cryoglobulinemia, polyarteritis nodosa, Wegener's granulomatosis, infection, and collagen vascular diseases. The culprit drugs should be recognized and promptly withdrawn. Drugs introduced within 2 mo are suspect. Systemic corticosteroids may be of some benefit in severe reactions.

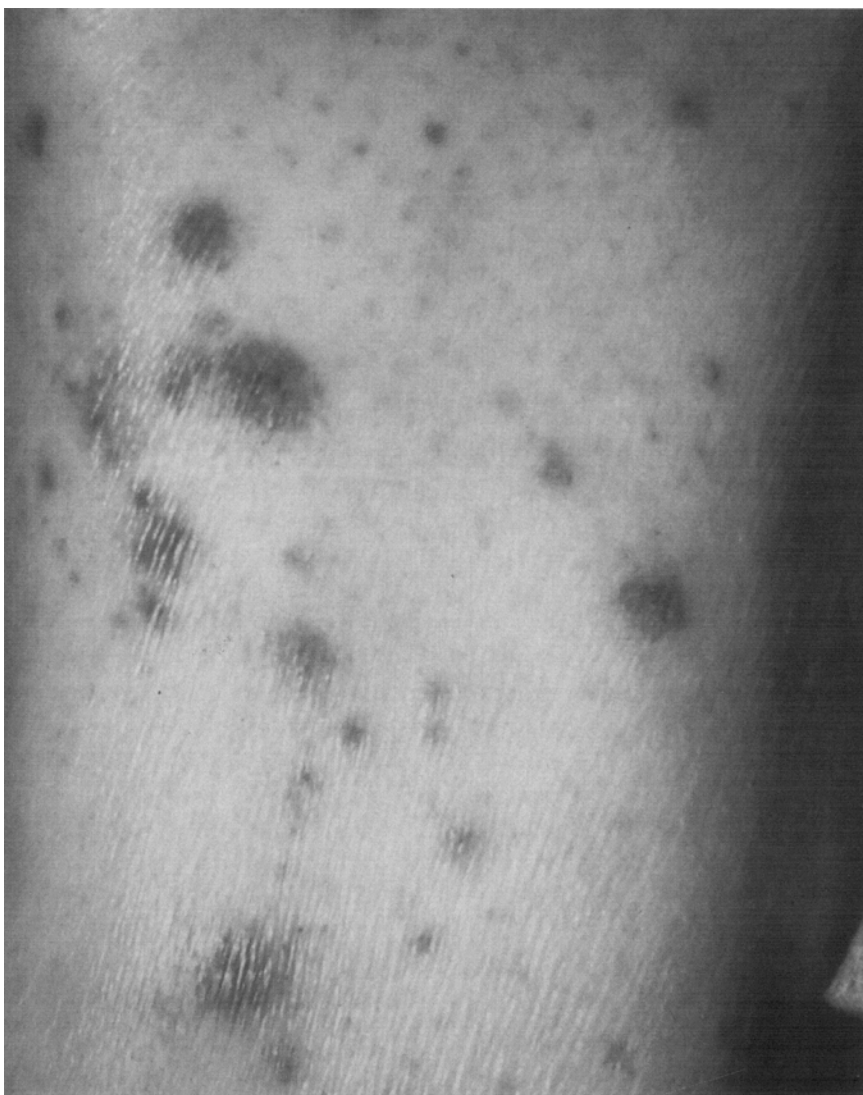


Fig. 5. Drug-induced vasculitis.

Angioedema (54)

Nosology, Pathophysiology, Clinical Features, and Differential Diagnosis

Immediate hypersensitivity reactions constitute a wide spectrum from mild pruritus and urticaria to systemic anaphylaxis that can result in shock and death. These reactions can involve any organ in

the body, with a predilection for pulmonary, circulatory, cutaneous, neurologic, and gastrointestinal systems. Systemic reactions include one or more forms of cutaneous involvement, such as pruritus, flushing, erythema, urticaria, and in severe cases, angioedema. In angioedema, congestion involves mucous membranes of the eyes, nose, and mouth and swelling of the lips or tongue that may impair swallowing and ventilation. Upper-airway obstruction may result from edema of the larynx, epiglottis, or surrounding tissues. Angioedema may be isolated without systemic involvement. Many mechanisms have been described leading to angioedema. A susceptible person is exposed to a foreign substance resulting in the generation of an IgE-antibody response. The secreted IgE antibody rapidly associates with high-affinity receptors on mast cells and basophils. During re-exposure, antigen induces the crosslinking and degranulation of these cells, releasing mediators, such as histamine. Another mechanism is activation of the complement cascade, resulting in the formation of anaphylatoxins by immune complexes or other agents. Certain agents, hyperosmolar solutions, such as mannitol and radiocontrast mediums, and nonsteroidal anti-inflammatory drugs can directly stimulate the release of mediators by an unknown mechanism independent of IgE or complement. For angiotensin-converting enzyme inhibitors, angioedema may be owing to the inhibition of kinin metabolism (55). Angioedema induced by insect stings or food or hereditary angioedema should be excluded.

Culprit Drugs in Angioedema

Among the causes of immediate hypersensitivity reactions, antibiotics (especially the penicillins) and radiographic contrast agents are the most common. The rate of serious anaphylactic reactions is about 1/5000 exposures, and <10% of such reactions are fatal. Other drugs frequently involved are angiotensin-converting enzyme inhibitors, nonsteroidal anti-inflammatory drugs, opiates, and curare. Among these drugs, angioedema induced by angiotensin-converting enzyme inhibitors is the major cause of hospitalization, occurring in 2–10/10,000 new exposures (56). Depending on the sensitivity of the person and the route, quantity, and rate of administration of the antigen, reactions may occur within minutes or hours; the vast majority occur within 1 h of exposure. For angiotensin-converting enzyme inhibitors, the risk is highest during the 3 wk after the onset.

Treatment of Angioedema

Severe forms of angioedema, because they are associated with upper-airway obstruction, or systemic symptoms of anaphylaxis

necessitate epinephrine sc injection (0.3–0.5 mL of 1 : 1000 dilution, i.e., 0.3–0.5 mg every 10–20 min) with eventually resuscitative efforts (intubation, iv fluids). To block or reduce prolonged or late-phase reactions, corticosteroids (250 mg of hydrocortisone or 50 mg of methyl prednisolone intravenously every 6 h for 2–4 doses) and/or antihistamines (25–50 mg of hydroxyzine or diphenhydramine intramuscularly or orally every 6–8 h as needed, 300 mg of cimetidine intravenously or orally every 6 h) are associated. Antihistamines and corticosteroids are not the drugs of choice in the initial treatment of an acute reaction, although both may be administered after treatment with epinephrine has stabilized cardiorespiratory symptoms. Of course, further administration and absorption of the suspected drug(s) must be discontinued. All patients who have serious angiodema should be hospitalized and monitored for at least 24 h, since relapses may occur.

Conclusion

Severe skin adverse drug reactions are rare (<1/1000 exposures). Treatment of these severe skin adverse drug reactions includes prompt recognition and withdrawal of suspected drugs and hospitalization in an dermatological intensive care unit where the patient will be managed. After recovery, patients should be advised to avoid not only the suspect drug(s), but also chemically related compounds. Finally, usual prescriptions of physicians should avoid high-risk drugs when they are not absolutely necessary.

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